Remarks

Claims 18-26, 28-53 are pending. Claim 27 has been canceled. Claims 52 and 53 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 33, 38, 42, 45, 48, 50 and 51 have been amended.

Priority

The disclosure was objected to for allegedly failing to set forth that the present application is a proper National Stage (35 USC § 371) entry of PCT Application No. PCT/EP03/11027 in the first paragraph of the specification or in an application data sheet. Applicants respectfully submit that there is no basis for this objection. The requirement for setting forth a priority claim in the first paragraph of the specification is based on the 35 U.S.C. § 120, wherein it states "An application for patent for an invention ... shall have the same effect, as to such invention, as though filed on the date of the prior application ... if it contains or is amended to contain a specific reference to the earlier filed application." However, there is no requirement for a PCT Application entering the U.S. National Stage to identify itself as such or claim priority to the PCT application from which it extends. In fact, MPEP § 1893.03(c) makes the following warning:

> Note: a national stage application submitted under 35 U.S.C. 371 may not claim benefit of the filing date of the international application of which it is the national stage since its filing date is the international filing date of the international application. See also MPEP § 1893.03(b). Stated differently, since the international application is not an earlier application (it has the same filing date as the national stage), a benefit claim under 35 U.S.C. 120 in the national stage to the international application is inappropriate and may result in the submission being treated as an application filed under 35 U.S.C. 111(a). See MPEP § 1893.03(a). Accordingly, **it is not necessary for the applicant to amend the first sentence(s) of the specification to reference the international application number that was used to identify the application during international processing of the application by the international authorities prior to commencement of the national stage.**

(emphasis added). Applicants therefore respectfully request the withdrawal of this objection.

Claim Objections

Claim 33 was objected to for failing to contain a period. Claim 38 was objected to based on the misspelling of the word "consisting." Claim 48 was objected to based on the misspelling of the word "DSM." Claims 33, 38, and 48 have been amended to correct these typographical errors.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 18-51 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. However, one determines undue experimentation not by analyzing a single factor, but rather by analyzing and weighing many factors. The legal standard set out in *In re Forman* 230 U.S.P.Q. 564, 547 (Bd. Pat. App. & Int. 1986) and elucidated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988) sets forth the following factors for consideration: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

The present claims are directed to the preparation of a cell capable of high yield expression of a target gene product having essentially human glycosylation patters. The original

claims cover all proteins using any immortalized human or human hybrid starting cell. The Office Action alleges that the method would not yield essentially human glycosylation patterns for all proteins using any immortalized human or human hybrid starting cell.

A. To support this position, the Office first argues based on teachings of Fussenegger et al. (A5 in IDS) that glycosylation is a post-translational event for secreted proteins, that glycosylation patterns are affected by many parameters such as sequence of the polypeptide chain, and that not all proteins are naturally glycoslylated, including those that are not normally secreted. In order to facilitate prosecution, Applicants have amended claim 18 to recite "wherein the target gene product is a secreted protein."

B. The Office Action further bases the rejection on the premise that glycosylation patterns are affected by the sequence of the polypeptide chain. The Office notes that Applicants place no limit on the amino acid sequence of the target gene product and alleges that altering the sequence to change the glycosylation pattern of the product would somehow be required to achieve the claimed result. Applicants respectfully disagree. While the specific glycosylation pattern of the target protein would be a function of its sequence, the essentially human nature of the glycosylation would not. As noted by the Office Action, the non-human glycosylation to be avoided is a function of the enzymes present in the cell. Thus, a human hybridoma will always produce an antibody with human glycosylation, regardless of the sequence of the antibody. As such, demonstration by Applicants that, for example, Leptin-Fc produced from PBG04 has essentially human glycosylation is sufficient evidence that other proteins produced by this cell line will likewise have essentially human glycosylation even if the actual pattern of glycosylation is drastically different.

C. The Office Action further posits that the claim would not be enabled even where the target protein is an antibody based on the allegation that mouse hybridomas, human hybridomas, myelomas, and hetero-hybridomas yield IgG chains with different glycosylation patterns. To support this position, the Office Action cites Yoo et al. (*J. Immun. Methods*. 261:1-20, 2002) for the alleged teaching that mouse-human hetero-hybridomas add a particular glycan to IgG where mouse NSO myelomas and rat myelomas do not. Moreover, Yoo et al. allegedly teaches that mouse-human hetero-hybridomas generally follow the glycosylation patterns of the mouse parental line. The Office appears therefore to be taking the position that knowledge of embodiments that do not have the preferred benefits of the claimed method is *prima facie* evidence of non-enablement. Applicants respectfully disagree.

To be enabled, there must simply be sufficient disclosure in the application such that the skilled artisan would be able to practice the invention without undue experimentation. Here, Applicants provided sufficient guidance in the specification based on the knowledge generally available in the art for the skilled artisan to select cells, such as a human-mouse hetero-hybridoma, that would produce proteins with desired glycosylation. The specification makes it clear that the skilled artisan should preferably use cells that provide the necessary enzymes to generate human-specific modifications and lack enzymes which are not present in human cells and are responsible for atypical linkages (see paragraph [0064] of published application). In addition to using cells that are entirely human, the specification provides guidance in using cells with a subset of human chromosomes wherein the human specific glycosylation enzymes dominate over the non-human enzymes (see paragraph [0064]).

For example, the fact that mouse cells contain the additional glycosylation enzyme alpha 1,3 galactosyltransferase, which as noted in Yoo et al. adds an additional terminal galactose with an α1,3 linkage that is strongly immunogenic in humans, was both known in the art and disclosed in the instant specification (see paragraph [0066]). Likewise, Applicants identified N glycolylneuraminic acid (NeuGc) as an immunogenic linkage to be avoided (see paragraph [0065]).

Thus, contrary to the position taken by the Office Action, the claimed method does not require that the skilled artisan be able to predict the final glycosylation pattern for any given cell. Instead, the skilled artisan need only have sufficient knowledge and guidance to avoid undesired, immunogenic glycosylation. For example, the specification provided guidance in the form of specific examples of hybrid cells, e.g., H-CB-P1 and PBG04, where expression products contained acceptable glycosylation for human use, e.g., 1.3% α1,3 galactose on leptin-Fc derived from PBG04.

Moreover, the skilled artisan would be able to use ordinary skill to screen expression products from candidate hetero-hybridomas based on this guidance provided. Importantly, this screening step would not require integrating the gene of interest into the candidate cell. Instead, the presence of undesired, immunogenic (non-human) glycosylation can be evaluated on native proteins (e.g., immunoglobulins) secreted by the cell. As discussed above, while the glycosylation pattern of the native protein would necessarily be different from that of the target protein, the presence or absence of non-human linkages, such as α1,3 galactose, would expectedly be consistent.

D. The Office Action further posits that the specification does not appear to include an example in which the claimed method is practiced. Specifically, the Office Action notes that Applicants discuss the glycosylation of "leptin Fc from PBG04," but then alleges that it is not clear whether this product is a natural product of the PBG04 cell line or whether it is made from a particular targeting vector. Applicants respectfully disagree. The examples are directed to constructs containing the gene hOBFc, which the Office Action refers to as a "place holder gene." However, the skilled artisan would know that Leptin is encoded by the "obese (Ob)" gene (knocked-out in Ob/Ob mice) and that hObFc is a gene encoding a Leptin-Fc fusion protein. As such, the glycosylation patterns for Leptin-Fc examined in Example 5 represent an exemplification of the claimed method contrary to the allegation of the Office Action.

Furthermore, evidence that there was only 1.3% α1,3 galactose on leptin-Fc derived from PBG04 would be a reasonable indication that other proteins expressed using this method would also have low α1,3 galactose. This example is therefore evidence that the claimed method is in fact enabled and useful for producing therapeutic proteins.

Applicants therefore respectfully request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 18-51 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Office Action alleges that the phrase "high yield" expression in claim 18 is unclear. Applicants note, however, that this limitation is an inherent benefit of the recited steps. As such,

Applicants have amended claim 18 to delete this phrase. No new matter is added by this amendment.

The Office Action further alleges that the phrase "essentially human glycosylation pattern" in claim 18 is unclear. Applicants respectfully disagree. First, this phrase is in the preamble and is not a step of the claimed method. As such, the skilled artisan does not have to determine whether the expression product produced by the method does in fact have essentially human glycosylation in order to determine whether they infringe the claim, i.e., the purpose of the clarity requirement. Instead, this phrase is in the preamble and merely identifies a preferred use of the claimed method. The skilled artisan knows that non-human glycosylation linkages can be immunogenic in humans and thus limit the usefulness of a potential therapeutic product in humans. However, the threshold of these potentially immunogenic linkages may be different depending on how the product is intended to be used, e.g., acute vs. chronic illnesses, modes of administration, etc. Thus, the phrase "essentially human glycosylation pattern" is meant to convey to the skilled artisan the ability to limit the amount of non-human glycosylation (such as α1,3 galactose) while still maintaining the advantage of stable, high yield expression, which was previously unavailable in prior art human expression systems. Applicants respectfully request the withdrawal of this rejection.

The Office Action further alleges that the phrase "screening for the locus of the Ig gene within the genome of the starting cell" in step (b) of claim 18 and claim 42 is unclear. In order to facilitate prosecution, Applicants have amended claims 18 and 42 to delete step (b). The remaining steps have been re-numbered accordingly. The resulting step (b) has been further

amended to recite "replacing a gene coding for the Ig" based on the change in antecedent. No new matter is added by this amendment.

The Office Action has further alleged that the phrase "a known locus" in the claim 27 is unclear. In order to facilitate prosecution, Applicants have canceled claim 27.

The Office Action further alleges that the phrase "by use of a recombinase" in step (d) of claim 18 is unclear. Applicants have amended step (d) to clarify the active steps by which the second DNA sequence is integrated. No new matter is added by this amendment.

The Examiner has further alleged that it is not clear in claim 50 which light chain is being referenced. Applicants have amended claim 50 to provide this clarity. No new matter is added by this amendment.

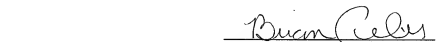
The Examiner has further alleged that claim 51 does not recite the steps that would result in the outcome in the preamble, i.e., yield expression of a target gene product. Applicants have amended claim 51 to recite "a method for producing a secreted target gene product" instead of "a method for high yield expression of a target gene product." No new matter is added by this amendment.

Conclusions

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment authorizing payment in the amount of $245.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(2) for a Two Month Extension of Time, and a Request for Extension of Time are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,



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